Case Reports

Prolactinoma in a Man Following Industrial Exposure to Estrogens

STEVEN H. BARON, MD, PhD
Sepulveda, California

JAMES R. SOWERS, MD
Richmond, Virginia

MILTON FEINBERG, MD
Van Nuys, California

THE CAUSE of pituitary tumors that secrete excess amounts of prolactin (prolactinomas) is uncertain, but there are substantial clinical and experimental data suggesting that estrogen may have an etiologic role.[1-5] A temporal link has been observed between the manifestations of hyperprolactinemia and estrogen-containing oral contraceptive use and childbirth.[1-5] However, others have observed only an equivocal temporal relationship between use of oral contraceptives and clinical presentation of prolactinomas.[6-10] In this report we describe a remarkable temporal relationship between industrial exposure to estrogen and the onset of hyperprolactinemia secondary to a prolactinoma in a man. To our knowledge, this is the first report of a temporal link between estrogen and the development of a prolactin-secreting pituitary tumor in a man.

Report of a Case

The patient, a 61-year-old man, was formerly employed by a pharmaceutical company that manufactures oral contraceptive pills. As a senior processing operator from 1971 to 1974, his duties included weighing and mixing norethindrone and mestranol, transporting the chemicals to and from mixing drums, ovens, storage facilities and tablet presses, and milling the chemicals into fine particles. During this work, he and his coworkers wore protective nylon suits and head coverings, but when they removed the garments they came into contact with the fine particles. Before beginning this particular job, the patient was told that he might develop "tender breasts." Of the dozen or so employees in his department, he noted that in most (both male and female) breast tenderness, "lumps" or enlargement developed. Furthermore, the patient knew of at least one male employee who had a mastectomy for breast enlargement.

Between 1972 and 1974, the patient noted bilateral breast swelling and nipple tenderness, and had intermittent episodes of impotence and diminished libido. In 1974 he complained of galactorrhea and gynecomastia, and was transferred to another department within the company. However, galactorrhea and gynecomastia persisted and in November 1975 a bilateral simple mastectomy was carried out. A prolactin level before the operation was 66 ng per dl. Because of the persistence of impotence and diminished libido, the patient was reevaluated in April 1976. Laboratory studies at that time gave the following values: thyroxine, 8.1 μg per dl; triiodothyronine, 167 ng per dl; thyroid stimulating hormone, 4.9 μU per ml; serum testosterone, 505 ng per ml; 24 hour urine study for 17-hydroxysteroids and ketosteroids, 7.6 mg and 5.7 mg, respectively, and serum prolactin, 68 ng per ml (normal, less than 30). Polytomography of the sella turcica showed an erosion in the floor of the sella into the left sphenoid sinus.

In September 1976 a transsphenoidal adenectomy

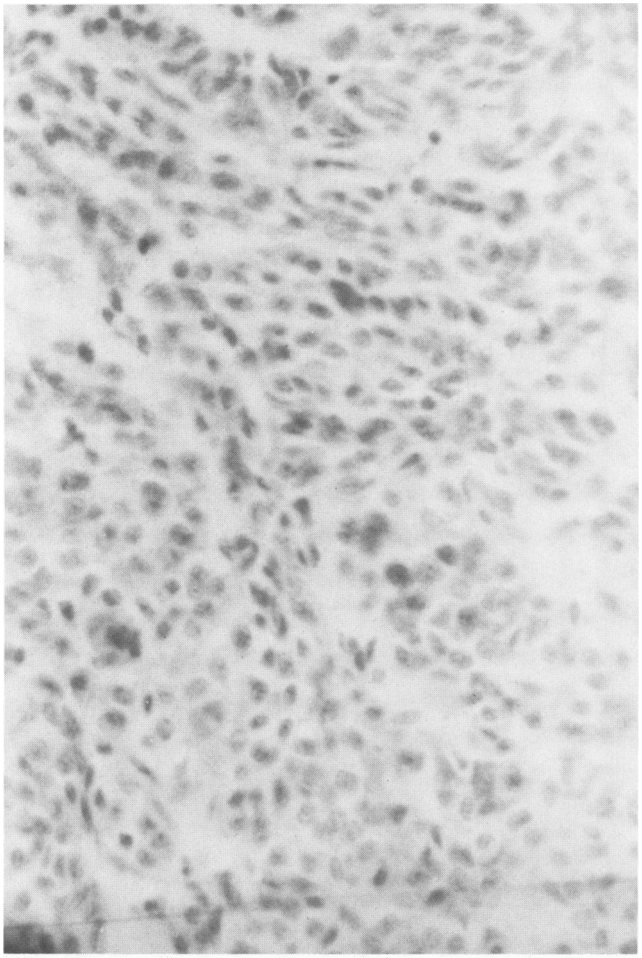

Figure 1.—Microscopic appearance of a prolactinoma in a man with clinical manifestations of hyperprolactinemia following industrial exposure to estrogens (reduced from ×200).

Refer to: Baron SH, Sowers JR, Feinberg M: Prolactinoma in a man following industrial exposure to estrogens. West J Med 1983 May; 138: 720-722.

From the Department of Medicine, UCLA-San Fernando Valley Medical Program, Sepulveda, California, and the Department of Pathology, Los Angeles County-Olive View Medical Center, UCLA Campus, Van Nuys, California.

Submitted, revised, July 8, 1982.

Reprint requests to James R. Sowers, MD, Division of Endocrinology, Veterans Administration Medical Center, Richmond, VA 23249.

was done. A microadenoma was seen and removed along with a rim of pituitary tissue. Viewed microscopically, the pituitary tissue contained a diffuse area of tumor composed of a single cell type; the cells had normal to oval nuclei with indistinct agranular cytoplasm (Figure 1). The cells were periodic acid-Schiff negative and the tumor was classified as a chromophobe adenoma. After the operation diabetes insipidus developed in the patient but subsequently resolved. He regained potency and libido within six months. He had normal anterior pituitary function postoperatively.

Discussion

Although we do not have absolute proof that the development of a prolactinoma in this man was caused by estrogen exposure, there is considerable evidence supporting such a relationship. First, the clinical manifestations of hyperprolactinemia occurred after estrogen exposure. Before this exposure he had had no galactorrhea, gynecomastia or sexual dysfunction. He had taken no medication and had no other diseases[8] that could account for the symptoms. Furthermore, it appears that the galactorrhea, impotence and diminished libido were related to the hyperprolactinemia, as the latter two symptoms disappeared following hypophysectomy. Decreased libido and impotence are well-documented manifestations of hyperprolactinemia in men.[11] The bilateral mastectomy precluded observation of any relationship between the prolactinoma and galactorrhea.

Data from large series of patients with prolactinomas suggest a circumstantial relationship between estrogen use and prolactinomas. Molitch and Reichlin compiled data from 14 separate series and noted that of the patients with prolactinomas in whom previous oral contraceptive use could be ascertained, more than half the patients (189 of 363; 52.1 percent) had received oral contraceptives.[1] In some series, the percentage of tumor-bearing patients exposed to oral contraceptives reached 60 percent to 80 percent.[2-5] Sherman and his associates have concluded that exogenous estrogens or estrogen secreted during pregnancy may have a stimulatory effect upon the growth of clinically silent prolactinomas in some patients.[4,8]

That estrogen administration to humans leads to hyperprolactinemia has been documented in hypogonadal[12] and eugonadal[13] females. During the hyperestrogenic state of pregnancy, hypertrophy and hyperplasia of pituitary lactotrophs occurs.[14,15] Although ours is the first report of a link between estrogens and prolactinoma development in a man, there has been a report of a man who took estrogen for a year in whom galactorrhea, oligospermia and hyperprolactinemia (45 to 83 ng per ml) developed but who had no radiographic evidence of a pituitary tumor and whose prolactin levels declined following cessation of estrogen administration.[16]

There is substantial evidence that estrogen not only enhances prolactin secretion but also induces pituitary growth in animals. The former action of estrogen may be due to both a direct pituitary effect as well as an indirect effect via the hypothalamus to inhibit prolactin inhibitory factor. For example, estrogen has been shown in rat and ovine pituitary tissue to increase the incorporation of precursors into prolactin,[17-19] the accumulation of preprolactin in ribonucleic acid (RNA)[18-20] and prolactin synthesis.[18-22] In addition to these direct stimulatory effects upon the pituitary, estrogen decreases prolactin-inhibiting activity[23] and the release of the prolactin-inhibiting factor dopamine.[24] In regard to pituitary growth, a single injection of diethylstilbestrol into male rats is associated with pituitary hyperplasia or tumor in 70 percent of the animals.[25]

Conclusion

We believe there is reasonable clinical and experimental evidence suggesting a causal relationship between our patient's exposure to estrogens and the development of a prolactinoma. Thus, estrogen exposure may have either initiated tumor growth, or stimulated growth of a clinically silent microadenoma. That clinically silent pituitary microadenomas are not uncommon has recently been documented in an autopsy series.[26] Our case report emphasizes the fact that men, as well as women, exposed to industrial or other sources of estrogens need to be under surveillance for the development of clinical manifestations of hyperprolactinemia and pituitary tumors. Finally, measures to reduce industrial exposure to estrogens appear to be warranted.

REFERENCES

1. Molitch ME, Reichlin S: The amenorrhea, galactorrhea, and hyperprolactinemia syndromes. Adv Intern Med 1980; 26:37-65

2. Post KD, Biller BJ, Adelman LS, et al: Selective transsphenoidal adenomectomy in women with galactorrhea-amenorrhea. JAMA 1979 Jul; 242:158-162

3. Shearman RP, Fraser IS: Impact of new diagnostic methods on the differential diagnosis and treatment of secondary amenorrhea. Lancet 1977; 1:1195-1197

4. Sherman BM, Schlechte J, Halmi NS, et al: Pathogenesis of prolactin-secreting pituitary adenomas. Lancet 1978; 2:1019-1021

5. Chang RJ, Keye WR Jr, Young JR, et al: Detection, evaluation, and treatment of pituitary microadenomas in patients with galactorrhea and amenorrhea Am J Obstet Gynecol 1977; 128:356-363

6. Kleinberg DL, Noel GL, Franta AG: Galactorrhea: A study of 235 cases, including 48 with pituitary tumors. N Engl J Med 1977; 296:589-593

7. Conlam CB, Annergers JF, Abbond CF, et al: Pituitary adenoma and oral contraceptives: A case-control study. Fertil Steril 1979; 25-28

8. Wingrave S, Kay CR, Vessey MP: Oral contraceptives and pituitary adenomas. Br Med J 1980 Mar; 280:685-686

9. Fayez JA, Sowers JR: Evaluation and treatment of patients with prolactin-secreting pituitary tumors. Int J Gynaecol Obstet 1980 Mar-Apr; 17:421-427

10. Tiperman L, Futterweit W, Zappulla R, et al: Oral contraceptive history as a risk indicator in patients with pituitary tumors with hyperprolactinemia: A case comparison of twenty patients. Neurosurgery 1980; 7:571-573

11. Carter JN, Tyson JE, Tolis G, et al: Prolactin-secreting tumors and hypogonadism in 22 men. N Engl J Med 1978; 299:847-852

12. Yen SSC, Ehara Y, Siler TM: Augmentation of prolactin secretion by estrogen in hypogonadal women. J Clin Invest 1974; 53:652-655

13. Vekemans M, Robyn C: The influence of exogenous estrogen on the circadian periodicity of circulating prolactin in women. J Clin Endocrinol Metab 1975; 40:886-889

14. Rigg LA, Lein A, Yen SSC: Pattern of increase in circulating prolactin levels during human gestation. Am J Obstet Gynecol 1977; 129:454-456

15. Yen SSC: Physiology of human prolactin, *In* Yen SSC, Jaffe RB (Eds): Reproductive Endocrinology, Physiology, Pathophysiology, and Clinical Management. Philadelphia, WB Saunders, 1978, p 163

16. Draznin B, Maman A: Estrogen-induced galactorrhea in man. Arch Intern Med 1979; 139:1059-1060

17. Maurer RA, Gorski J: Effects of estradiol-17β and pimozide on prolactin synthesis in male and female rats. Endocrinology 1977; 101:76-84

18. Shupnik MA, Baxter LA, French LR, et al: *In vivo* effects of estrogen on ovine pituitaries: Prolactin and growth hormone biosynthesis and messenger ribonucleic acid translation. Endocrinology 1979; 104: 729-735

19. Vician L, Shupnik M, Gorski J: Effects of estrogen on primary ovine pituitary cell cultures: Stimulation of prolactin secretion, synthesis, and preprolactin messenger ribonucleic acid activity. Endocrinology 1979; 104:736-743

20. Stone RT, Maurer RA, Gorski J: Effect of estradiol-17β on preprolactin messenger ribonucleic acid activity in the rat pituitary gland. Biochemistry 1977; 16:4915-4920

21. Nicoll CS, Meites JM: Estrogen stimulation of prolactin production by rat adenohypophysis *in vitro*. Endocrinology 1962; 70:272-277

22. Leiberman ME, Maurer RA, Gorski J: Estrogen control of prolactin synthesis *in vitro*. Proc Natl Acad Sci USA 1978; 75:5946-5949

23. Ratner A, Meites J: Depletion of prolactin-inhibiting activity of rat hypothalamus by estradiol or suckling stimulus. Endocrinology 1964; 75:377-382

24. Cramer OM, Parker CR Jr, Porter JC: Estrogen inhibition of dopamine release into hypophysial portal blood. Endocrinology 1979; 104:419-422

25. Jacobi J, Lloyd HM, Meares JD: Induction of pituitary tumors in male rats by a single dose of estrogen. Horm Metab Res 1975; 7:228-230

26. Burrow GN, Wortzman G, Rewcastel NB, et al: Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. N Engl J Med 1981; 304:156-158

Noninvasive Diagnosis of Left Atrial Myxoma

DEBRA S. ECHT, MD
DIANA F. GUTHANER, MD
NORMAN BLANK, MD
RICHARD L. POPP, MD
Stanford, California

WITH THE ADVENT of M-mode and two-dimensional real-time echocardiography, the diagnosis of intracardiac tumors has commonly been made preoperatively and antemortem.[1-9] Several other noninvasive tests such as gated radionuclide cardiac imaging and computerized tomography (CT) scanning have been used.[10,11] We report the case of a patient in whom an abnormality was first considered from review of the chest films and the diagnosis confirmed by a two-dimensional echocardiogram and supported by dynamic CT scanning.

Report of a Case

A 44-year-old woman first presented to Stanford University Medical Center 16 years ago with Hodgkin's disease. She was staged as IIIA with bilateral cervical, supraclavicular, mediastinal and abdominal paraaortic node involvement. Treatment with low-dosage radiotherapy (total, 3,000 rads) to the affected lymphatic regions was successful, and she remained without evidence of disease when seen for yearly follow-up through October 1980. Although asymptomatic, her chest roentgenograms from 1978 through 1980 showed features of progressive pulmonary vascular congestion and enlargement of the main pulmonary artery. The diagnosis of congestive heart failure with secondary pulmonary hypertension was considered, as well as the possibility of recurrent mediastinal or hilar Hodgkin's disease masquerading as heart disease. Oral administration of furosemide was empirically begun. Conventional three-second CT scanning through the thorax showed no evidence of lymph node enlargement or tumor. The patient was referred to the Cardiology Division for evaluation of the cardiopulmonary abnormalities seen radiographically. She said she had no specific cardiac symptoms of congestive heart failure, syncope or chest pain. In addition, she stated she did not have weight loss, anorexia, fever, chills, rash or arthralgias.

On physical examination she was afebrile and had a heart rate of 100, blood pressure of 120/74 mm of

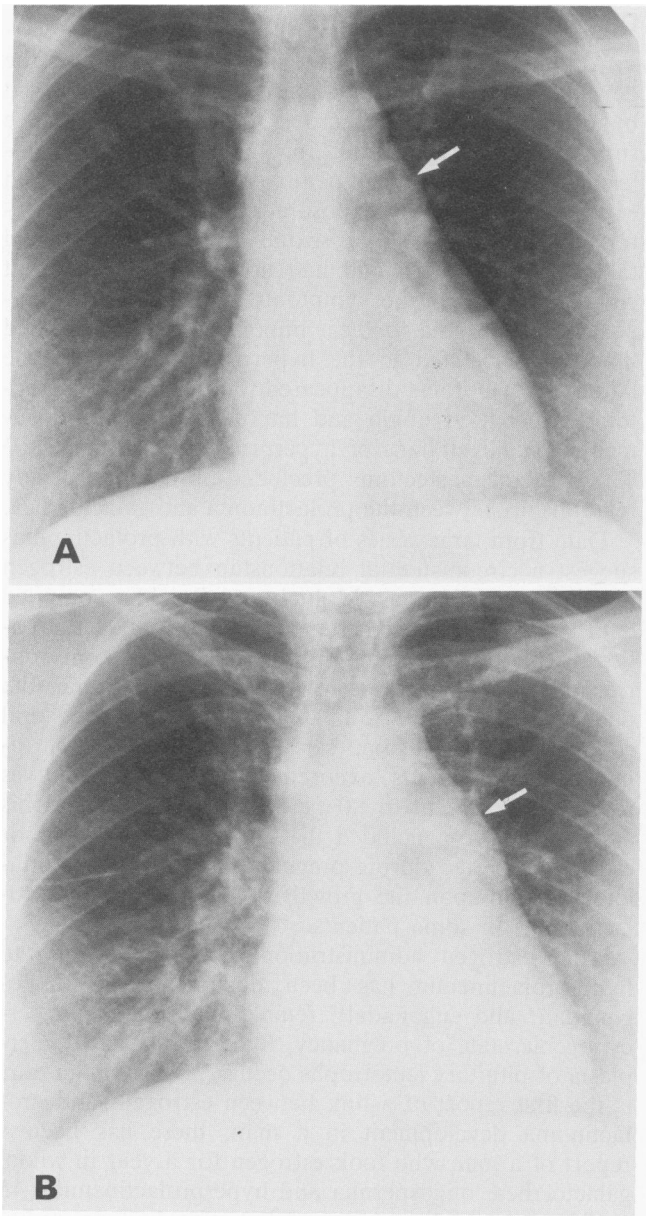

Figure 1.—Chest radiograph taken in September 1978 shows **(A)** the early changes of pulmonary venous hypertension with reversal of pulmonary blood flow to the upper zones and lack of clarity of the lower zone pulmonary vessels. Fullness of the pulmonary artery segment is evident **(arrow). (B)** Chest film in October 1980 shows changes of interstitial pulmonary edema indicating progression of pulmonary venous hypertension. Pulmonary artery segment has enlarged further **(arrow).**

Refer to: Echt DS, Guthaner DF, Blank N, et al: Noninvasive diagnosis of left atrial myxoma. West J Med 1983 Apr; 138:722-725.

From the Cardiology Division, Department of Medicine, and Department of Radiology, Stanford University Medical Center.

Submitted, revised, March 31, 1982.

Reprint requests to Richard L. Popp, MD, Cardiology Division, Stanford University Medical Center, Stanford, CA 94305.